Cannabis use and related clinical variables in patients with obsessive-compulsive disorder

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Abstract

Objective. Limited studies have investigated cannabis use in patients with obsessive-compulsive disorder (OCD), despite its widespread use by patients with psychiatric illnesses. The aim of this study was to assess the frequency, correlates, and clinical impact of cannabis use in an Italian sample of patients with OCD.

Methods. Seventy consecutive outpatients with OCD were recruited from a tertiary specialized clinic. To assess cannabis-related variables, patients completed a questionnaire developed for the purpose of this study, investigating cannabis use-related habits and the influence of cannabis use on OCD symptoms and treatments. A set of clinician and self-reported questionnaires was administered to measure disease severity. The sample was then divided into three subgroups according to the pattern of cannabis use: "current users" (CUs), "past-users" (PUs), and "non-users" (NUs).

Results. Approximately 42.8% of patients reported lifetime cannabis use and 14.3% reported current use. Approximately 10% of cannabis users reported an improvement in OCD symptoms secondary to cannabis use, while 23.3% reported an exacerbation of anxiety symptoms. CUs showed specific unfavorable clinical variables compared to PUs and NUs: a significant higher rate of lifetime use of tobacco, alcohol, and other substances, and a higher rate of pre-OCD onset comorbidities. Conversely, the three subgroups showed a similar severity of illness.

Conclusion. A considerable subgroup of patients with OCD showed a predisposition towards cannabis use and was associated with some specific clinical characteristics, suggesting the need for targeted consideration and interventions in this population.

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1. Introduction

Obsessive-compulsive disorder (OCD) is a prevalent and highly disabling psychiatric illness responsible for a substantial reduction in quality of life and a significant functional impairment for patients and their caregivers.[1–3]

Available treatments for OCD are at times only partially successful and treatment resistance might be a reason for patients' drop-outs with conventional medications.[4] In some circumstances, patients might use alternative substances to self-medicate or to cope with OCD symptoms. Among these, cannabis is the most widely used substance of abuse in the United States among youths and adolescents, due to its easy availability and affordable price. In a general population survey conducted in the USA, 1-year prevalence of cannabis use amounted to 34.5% of adults between 18 and 25 years old.[5] In a cross-national study, the prevalence of cannabis use disorder in Italian adolescents reached 2.77%, with a slightly higher rate in males than females (3.49% vs 2.09%).[6] Considering patients with OCD typically manifest the first symptoms during the school age,[7] these data might suggest an overlap of OCD and cannabis use in terms of age distribution, with young subjects being the most affected in both disorders.

Conventionally, impulsivity is the most important dimension involved in substance use disorders.[8] However, compulsivity has been recently proposed as a determinant of addiction,[9] being a common feature of OCD, as suggested by neurological and neuropsychological mechanisms coexisting in these disorders.[10,11] On the other hand, several studies exploring brain models of addiction and risk-oriented behaviors underlined the presence of high impulsivity in patients with OCD.[12–14] This characteristic is somehow opposite to personality traits

characterized by harm-avoidance typically expressed by patients with OCD[15–17] which, in turn, might discourage patients with OCD from involving themselves in potentially dangerous and unsafe situations often connected to substance use. Overall, substance use in OCD might be considered a result of a complex overlay and interplay of compulsivity, impulsivity, personality traits, and likely other dimensions whose roles need to be further investigated.

Previous investigations sought to describe the correlation between cannabis use and OCD. First, evidence from both animal and human studies suggests that the endocannabinoid system may play a role in OCD and related disorders.[18] A recent study, based on data from an online survey, assessed patterns of cannabis use in a large sample of individuals with a diagnosis of OCD ($N = 601$, based on a self-reported prior diagnosis by a healthcare profession or well-established cutoff on the OCI-R).[19] 42% of participants with OCD met cannabis use disorder criteria and nearly 70% for problematic cannabis use. Among negative factors associated with cannabis use, most participants were not currently receiving evidence-based OCD treatment, and the likelihood of this treatment decreased as cannabis use frequency increased.

Deepening the correlation between cannabis and OCD, some investigations reported cannabis use as a potential harmful factor for OCD. One study that primarily investigated prevalence, correlates, and predictors of OCD in a large (N = 390) birth cohort showed that a history of substance use disorder (cannabis/alcohol) was a prospective risk factor for OCD.[20] Challenging this finding, a prospective study in an adult population, recruited through a national survey, showed that cannabis use at baseline was unrelated to an increased risk of OCD diagnosis within 3 years of follow-up.[21] On the other hand, some investigations collecting cannabis users reported how OC symptoms severity predicted more frequent cannabis use.[22,23]

Furthermore, the effect of cannabis on OC symptoms has been investigated in some studies. Thus far, there have been only two small cannabinoid trials in individuals with OCD. With the limitation of a small sample (12 patients with OCD), a placebo-controlled investigation of different concentrations of tetrahydrocannabinol and cannabidiol suggested that smoked cannabis has a little acute impact on OC symptoms, compared to placebo.[24] In the second trial, 11 patients received nabilone over 4 weeks showing little effect on OC symptoms.[25] Conversely, the recent online survey from Kayser and colleagues[19] reported a relevant amount of participants (68.3%) experienced cannabis typically improved their obsessions to varying degrees, while a subset reported that cannabis worsened obsessions (17.3%) or compulsions (13.8%). Another study including 87 individuals self-identifying with OCD, measured (as tracked with a mobile app) a 60% reduction in compulsions and a 49% reduction in intrusions from before to after inhaling medical cannabis.[26] Other evidence of the effect of cannabis on OC symptoms is based on case reports, which showed a variable degree of improving after receiving dronabinol, a synthetic oral form of THC[27,28] or medicinal cannabis treatment.[29]

Although the results of this sparse literature suggest a possible link between OCD and cannabis use, to the best of our knowledge only limited studies have primarily investigated cannabis use in patients with OCD. In addition, the favoring role of specific sociodemographic or clinical features in cannabis users has not been investigated. Therefore, the primary aim of this study was to describe, in an Italian sample of patients with OCD, the frequency, correlates, and predictors of cannabis use and its impact on OC symptoms and on prescribed medications. Additionally, we wanted to stratify the sample according to the degree of cannabis use. We hypothesized that patients with sustained cannabis use would manifest more unfavorable sociodemographic and clinical characteristics compared with patients with discontinuous use or who never use this substance. This work is part of an international multicenter study in collaboration with the Department of Psychiatry and Behavioral Neuroscience at McMaster University in Canada and the present report illustrates the preliminary results of the Italian sample.

2. Methods

2.1. Participants

This retrospective and observational study was conducted at "Luigi Sacco" University Hospital in Milan, Italy. Patients with OCD were recruited from a tertiary psychiatric service dedicated to the diagnosis and treatment of outpatients with OCD. Recruitment took place between May 2019 and September 2021.

Inclusion criteria were: adult subjects (over age 18 years) with a diagnosis of OCD confirmed by trained psychiatrists through the administration of the Structured Clinical Interviews for DSM-5 (SCID), clinical version.[30] In case of psychiatric comorbidities, OCD had to be considered the primary disorder and directly responsible for OC symptoms. Exclusion criteria included brain diseases, intellectual disability, and psychiatric disorders secondary to a medical condition.

The study was conducted in accordance with the declaration of Helsinki.[31] Patients provided their written informed consent to participate in this study and to use their anonymized data for research purposes.

2.2. Measures

All patients were screened using a specific questionnaire developed for the purpose of the study, which was edited by the McMaster University Anxiety Working Group (through a collaboration of the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS)). This questionnaire specifically investigated the frequency and related features of cannabis use in a clinical population of patients with OCD (see Supplementary material for the extended version). The questionnaire comprises 34 questions administered at baseline by specifically trained research investigators. The first part of the questionnaire collected sociodemographic variables, including gender, age relationship status, ethnicity, living situation, highest level of education achieved, and occupational status. The second section focused on current and previous treatments for OCD (including psychotropic medications and psychotherapeutic approaches) assessing the perceived effectiveness and the reasons for discontinuation of previous treatments. The third section of the questionnaire investigated current and past use of any substance of abuse. Additional questions focused on cannabis use-related habits. In particular, the following information was collected: type of cannabis used (dried leaves or flowers, oils, edible, tinctures), frequency of use in the past week, average amount of cannabis consumed during a typical use and amount of cannabis consumed daily. Additionally, patients were asked to report if they were prescribed cannabis to treat OCD symptoms or another medical condition. The last questions focused on the influence of cannabis use on OCD symptoms (eg, improving or worsening OCD symptomatology after cannabis use) and on OCD treatments (eg, use of cannabis to treat OCD symptoms instead of a prescribed medication/psychotherapy).

Additionally, to assess patients' clinical picture at study entry, the questionnaire comprises three validated self-reported questionnaires: the Obsessive-Compulsive Inventory-Revised to measure obsessive-compulsive traits (OCI-R),[32] the 9-item Patient Health Questionnaire to measure depressive symptoms (PHQ-9),[33] and the Generalized Anxiety Disorder-7 scale to assess symptoms of general anxiety (GAD-7).[34]

Patients' medical records were analyzed to integrate additional clinical variables, in particular age at illness onset (AAO), age at first treatment, duration of untreated illness (DUI, defined as the time interval—in months—elapsing between the onset of the disorder and the administration of the first adequate psychopharmacological treatment), psychiatric comorbidities (pre-existing or occurring after the onset of OCD), and family history of psychiatric disorders. OCD symptoms severity was assessed at study entry by trained clinicians also through the administration of the Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS).[35]

2.3. Statistical analysis

Descriptive analyses of socio-demographic and clinical variables were performed for the whole sample. Additionally, descriptive analyses of habits related to cannabis use were performed in the subgroup of patients who reported current or lifetime cannabis use.

To stratify the sample according to the degree of cannabis use, we adopted the following criteria, which were previously adopted in an ICOCS study investigating cigarette smoking in patients with OCD[36]: "current users" (CUs), ie, patients who used cannabis within 6 months prior to study entry; "past users" (PUs), ie, patients who used cannabis in their lifetime but discontinued at least 6 months before receiving the questionnaire; and "non-users" (NUs), ie, patients who had never used cannabis in their lifetime. This distribution ideally reflected different severities of cannabis use in terms of frequency and duration, where CUs were patients with a more sustained and severe form of substance use, compared with PUs that used cannabis in their past, and, lastly, compared with NUs who ideally did not share risk factors for cannabis use.

Nonparametric Kruskal–Wallis and chi-squared tests were used to compare the three subgroups with respect to continuous and categorical variables considering the non-normal distribution of these data. Statistical significance was set at $P < .05$. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26 software (IBM Corp.; Armonk, NY, USA).

3. Results

3.1. Sample description

Seventy consecutive patients were included in the study (females: 57%, mean age: 37.1 ± 13.4 years). Nearly all patients were identified as Caucasian (98%). Table 1 outlines the main socio-demographic and clinical features of participants.

3.2. Habits related to cannabis and other substances use

With respect to cannabis use, 40 subjects had never used cannabis in their life (NUs, 57.1%), while 30 patients (42.9%) had. Among those who had used cannabis, 20 subjects had not used cannabis 6 months prior to study entry (PUs, 28.6% of the total sample), while 10 patients (CUs, 14.3% of the total sample) were still using it.

With respect to other substances, 50% of patients reported a lifetime use of tobacco, 67.7% reported a lifetime use of alcohol, 40.8% a combination of cannabis and alcohol use, and 7.2% used other substances. Moreover, 19.9% of patients reported having used, in their lifetime, prescription medications (ie, painkillers, anxiolytics, sleep aids/sedatives, stimulants outside the therapeutic regimen, on higher doses or frequency). In the last 6 months, 37.1% of patients reported tobacco use, 58.5% alcohol, 12.8% a combination of cannabis and alcohol, and 10% prescription medications.

Focusing on the effect of substances use on OC symptoms, 30% the total sample reported to have consumed a substance with the purpose to treat or help managing OC symptoms. In particular, cannabis was used for this purpose in 10% of patients, alcohol in 15.7%, tobacco in 7.1%, and prescription psychotropic drugs in 8.5%. Among cannabis users, a minority (10%) reported that this substance had helped reducing OC symptoms, with an average satisfaction score of 1.4 ± 2.9 on a scale from 0 (not at all effective) to 10 (extremely effective). Further details on the impact of cannabis on OC symptoms revealed that one patient (3.3%) reported a reduction in the number of intrusive thoughts, one (3.3%) a cessation of obsessions, and one (3.3%) a decrease in general anxiety. On the other hand, 23.3% of cannabis users reported a worsening of OC symptoms because of their cannabis use, associated with an increase in general anxiety.

No patient reported to have used cannabis instead of their prescribed treatment for OCD. Additionally, no patient reported to have reduced their prescribed OCD medications dose because of cannabis use or went off of OCD treatment or chose to use only cannabis to treat their OC symptoms. Only one patient (1.4%) reported using a cannabis prescription for a different medical condition (ie, chronic pain) than OCD.

3.2.1. Comparison between current cannabis users, previous users, and non-users

Figures 1 and 2 outline significant differences between the three subgroups.

PUs and CUs showed a lower age (31 ± 10.6 and 31.4 ± 11.3 years, respectively) compared to NUs (41.4 ± 14.5, $P = .01$). No significantly differences emerged between the three subgroups with respect to gender, living situation, highest level of education achieved, employment, or relationship status.

Considering clinical variables, age at first treatment was significantly earlier for PUs and CUs (20.9 ± 5.2 years and 22.4 ± 5.3 years, respectively) compared to NUs (29.2 ± 12.2 years, $P = .033$).

With respect to comorbidities, a pre-OCD onset comorbidity was significantly more common in CUs (90%) compared to NUs (55%) and PUs (60%, $P = .033$). In detail, pre-OCD onset bipolar disorder II was significantly more frequent in CUs (20%) compared to PUs (0%) and NUs (2.5%, $P = .027$). The prevalence of post-OCD onset comorbid major depression emerged to be higher among NUs (32.5%) versus the other subgroups (PUs: 0% and CUs: 20%, $P = .015$). Considering current medications, NUs were treated more frequently with more than two psychotropic drugs (25%) compared to PUs and CUs (5% and 0%, respectively, $P = .045$).

Additionally, compared with NUs, PUs and CUs showed a more frequent use of substances other than cannabis. In particular, lifetime alcohol use emerged to be significantly more frequent in PUs (100%) and CUs (90%) than NUs (45%, $P < .001$) and this difference was confirmed when the question referred to the past

Table 1. Sociodemographic and Clinical Variables of the Whole Sample and in the Three Subgroups

Variables	All patients	NUs	PUs	CUs
Number (%)	70 (100)	40 (57.1)	20 (28.6)	10 (14.3)
Age (years, mean ± SD)	37.01 ± 13.8	**41.4 ± 14.5**	**31 ± 10.6**	**31.4 ± 11.3**
Female gender (%)	57.1	55	55	83.3
Education (%)				
Secondary school	14.3	7.5	25	20
High school	54.3	55	55	50
University	31.4	37.5	20	30
Employment (%)				
Unemployed	24.5	27.5	20	20
Employed	55.7	55	65	40
Student	20	17.5	15	40
Co-habitation (%)				
Alone	15.7	17.5	15	10
Family	42.9	40	50	40
Family of origin	40	42.5	35	50
In a stable relationship (%)	52.9	45	65	60
Age of onset (years)	21.1 ± 10.6	24.1 ± 12.2	17.7 ± 5.8	16.3 ± 7.9
<18 years (%)	42.9	37.5	40	70
Age at first treatment (years)	25.7 ± 10.4	**29.2 ± 12.2**	**20.9 ± 5.2**	**22.4 ± 5.3**
DUI (months)	58.8 ± 81.4	61.9 ± 89.7	43.8 ± 75.6	77.3 ± 57
Y-BOCS	21.5 ± 9.5	17.6 ± 10.1	19.9 ± 8	24.3 ± 7.3
OCI-R	23.8 ± 12.6	22.6 ± 11.7	27.3 ± 15.1	21.2 ± 9.9
PHQ-9	11 ± 6	10.6 ± 6.5	11.2 ± 5	12.2 ± 6.2
GAD-7	9.7 ± 5.4	8.9 ± 5.8	11.2 ± 4.9	10.1 ± 3.9
Family history of psychiatric disorder (%)	64.3	57.5	75	70
Psychiatric comorbidities (%)				
Pre-onset (any)	65.7	**55**	**60**	**90**
Bipolar disorder II	4.3	**2.5**	**0**	**20**
Post-onset (any)	65.7	70	55	70
Major depression	21.4	**32.5**	**0**	**20**
Tourette syndrome	8.6	2.5	15	20
Current medication (%)				
Antidepressants	90	90	95	80
Antipsychotics	28.5	37.5	15	20
Mood stabilizers	7.1	7.5	5	10
Psychotherapy	17.1	12.5	25	20
Polytherapy (> 2 drugs)	15.7	**25**	**5**	**0**
Substance use lifetime (%)				
Cannabis	42.9	0	100	100
Tobacco	50	**32.5**	**75**	**70**
Alcohol	67.1	**45**	**100**	**90**
Other substances	82.8	**70**	**100**	**100**
Non-prescription medications	19.9	22.5	10	30

Table 1. *Continued*

Variables	All patients	NUs	PUs	CUs
Substance use past 6 months (%)				
Cannabis	14.2	0	0	100
Tobacco	37.1	**22.5**	**50**	**70**
Alcohol	51	67.5	75	90
> 1 alcoholic drink daily (%)	22.8	**10**	**35**	**50**
Substance use to cope with OC symptoms (%)				
Cannabis	14.2	0	0	100
Alcohol	15.7	**5**	**25**	**40**

Note: Values for categorical and continuous variables are expressed in percentages and mean ± standard deviation (SD), respectively. Bold indicates a statistically significant difference.
Abbreviations: CUs: current cannabis users; NUs: non-cannabis users, PUs: past cannabis users; DUI: duration of untreated illness; GAD-7: General Anxiety Disorders Scale; OCI-R: Obsessive-Compulsive Inventory-Revised; PHQ-9: Patient Health Questionnaire; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.
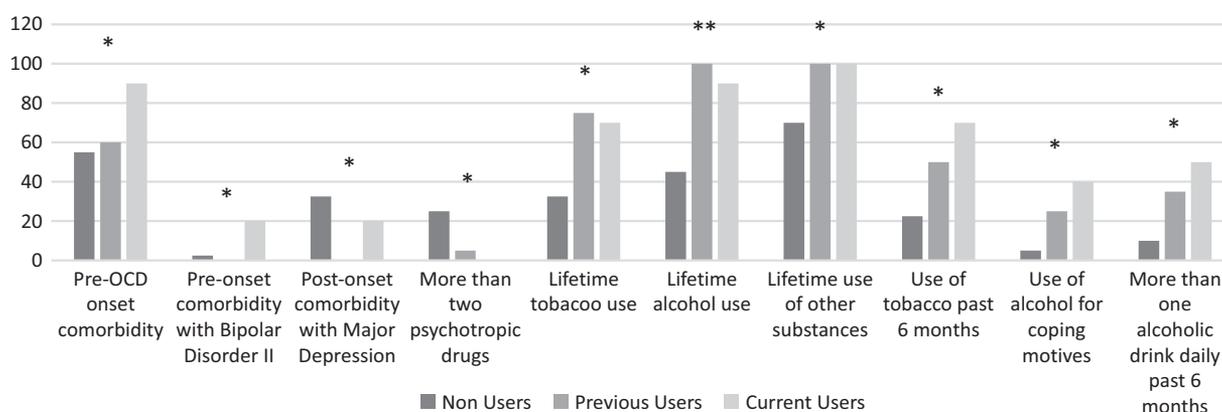
Figure 1. Statistically significant categorical variables in the comparison between non-users, previous users, and current users of cannabis. Values for categorical variables are expressed as %. OCD: obsessive-compulsive disorder; statistics: *: $P < .05$; **: $P < .001$.
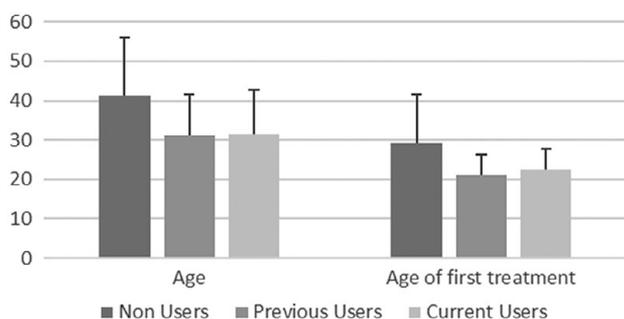
Figure 2. Statistically significant continuous variables in the comparison between non-users, previous users, and current users of cannabis. Values for continuous variables are expressed as mean ± standard deviation; statistics: *: $P < .05$.

6 months, although not at a significant level (PUs: 75.0%, CUs: 90%, NUs: 67.5%). Moreover, PUs (35%) and CUs (50%) reported to have consumed more frequently more than one alcoholic drink daily compared to NUs in the past 6 months (10%, $P = .034$). Considering the use of alcohol as a coping strategy for OC symptoms, PUs and CUs (25% and 40%, respectively) reported the use of alcohol as self-medication more frequently than NUs (5%, $P = .01$). With respect to tobacco use, similar results emerged. Lifetime tobacco use was significantly more frequent in PUs (75%) and CUs (70%) than NUs (32.5%, $P = .003$); the same difference

emerged also for the previous 6 months (CUs: 70% vs PUs: 50% vs NUs: 22.5%, $P < .001$). Lifetime use of at least one other substances of abuse (ie, cocaine, amphetamine/methamphetamine, inhalants, hallucinogens, or heroin) was significantly higher in CUs (100.0%) and PUs (100%) compared to NUs (70%, $P = .004$).

4. Discussion

In the present sample, 42.8% of patients with OCD reported lifetime cannabis use (PUs plus CUs). This percentage is understandably higher compared to a previous general population survey that indicated 1-year cannabis use in 34.5% of young adults,[5] being likely related to the different periods of time that were investigated (lifetime vs 1 year, respectively). Among patients who had used cannabis, 14.2% reported cannabis use in the 6 months prior to study entry (CUs), reflecting more sustained and habitual use. Our results seem to underestimate the use of cannabis in patients with OCD if comparing to the recent study from Kayser and colleagues,[19] where nearly 90% of participants reported using cannabis at least 1 day over the previous month and nearly 60% reported using cannabis at least daily. This latter study was conducted in the USA which shows an increasing access to cannabis both for recreational and therapeutic uses compared to European countries, and, additionally, the data could have been biased since only participants with at least one lifetime use of cannabis were recruited in the survey.

With respect to other substances, a considerable number of patients investigated in the present study reported lifetime use of tobacco and alcohol (50% and 67.1%, respectively). Comparing our findings with previous studies (reporting rates ranging between 7% and 22.4%[37,38]), we found an overall higher rate of smoking habits (50%). Cigarette smoking in outpatients with OCD has been studied in a previous report from the ICOCS, showing a cross-sectional prevalence of 24.4% in the sample, and tobacco smokers were more frequently associated with comorbidity with Tourette' syndrome and tic disorder and with a higher number of suicide attempts.[36] A recent systematic review, aimed at assessing the therapeutic use of nicotine on OC symptoms, showed some efficacy in treatment-refractory patients with OCD.[39] Therefore, tobacco might be potentially used by more severe patients as a self-medication strategy. The prevalence of alcohol use disorder in OCD differs among recent studies (rates ranging from 7.5% to 20%)[40–42] and has been associated with compulsivity trait,[43] male gender, and an increased risk of suicide.[41] Additionally, in our sample around two out of 10 patients reported lifetime use of other non-prescription medications (19.9%) and other substances of abuse (7.2%). These data seem to support a certain predisposition towards substance use in patients with OCD. This phenomenon has been investigated and debated in the literature, with controversies about its reasons and frequency.[44] On one hand, OCD is phenomenologically characterized by compulsivity and impulsivity[12] that would drive affected individuals to use substances while, on the other hand, patients with OCD often show a harm-avoidance phenotype, which would elicit the opposite effect. The prevalence of a full-blown substance use disorder varied extensively in previous literature investigations, from 1% (in an international multicenter study carried out on community samples of patients with OCD[45]) to 11% (in a large Danish population study[46]). These differences are probably related to different sampling procedures. In a cross-sectional population survey conducted in the Netherlands, the life-time and 12-month odds of being diagnosed with a substance use disorder in subjects with OCD was significantly higher than the odds for people without a psychiatric disorder and, in men, the co-occurrence of substance dependence and OCD was significantly higher than the co-occurrence of substance dependence and any other psychiatric disorders.[47] On the contrary, the hypothesis that OCD and substance use are not related emerged in some studies showing that both alcohol and drug misuse disorders were not significantly associated with OCD.[48] In another report, moreover, substance use disorder was half as common in patients with OCD than in the general population.[49] These mixed results underline the need to further investigate the reasons behind substance use in OCD which may be related to different comorbidity profiles and trajectories of OCD course.

In this light, the present study showed that 30% of patients with OCD used a substance of potential abuse during their lifetime to treat or to help manage their symptoms. In particular, alcohol was the most used substance for this purpose (15.7%), followed by cannabis (10%), other prescription medications (8.5%), and tobacco (7.1%). A minority of cannabis users (10%) reported that this substance has helped treat OCD symptoms (in reducing the number of obsessions or levels of general anxiety), even if they considered this effect minimal (average level of satisfaction around 2 on a scale from 0 to 10). Interestingly, no improvements in compulsions were reported. On the other hand, 23.3% of cannabis users reported a worsening of OCD symptoms because of cannabis use (ie, increase of general anxiety). Even though the limited sample size did not allow us to discover if an effect was more frequent than the other, we could state these effects were not univocal among patients. In the Italian culture, cannabis is often used as an illicit substance outside of government authority's control, although the recent legalization of medical cannabis has not, so far, lead to cannabis being indicated as a treatment for anxiety disorders. Consequently, it is not surprising that the effects of cannabis use were different, presumably also reflecting the variability of concentration of phytocannabinoids, the different administrations, the amount of substance consumed on one occasion, and the frequency and total period of use.[50] Indeed, patients with OCD might decide to experiment with cannabis due to the partial efficacy of conventional medications (in our sample treatment satisfaction was around 6.5 on a scale from 1 to 10). However, we observed that no patient used cannabis to reduce or stop the therapy already prescribed by their treating psychiatrist. Nonetheless, the social perception related to the effect of cannabis might have led to the cannabis use as a coping strategy to handle anxiety or OC symptoms. Relaxation and tension reduction were the most commonly reported effects of cannabis use in previous investigations that demonstrated a positive effect of cannabis use for anxiety[51,52] and other psychopathological dimensions (ie, to cope).[53–55]

Considering the second aim of the present study, our hypothesis that patients who used cannabis were clinically more severe was supported by the higher frequency of more severe clinical variables in cannabis users. First, CUs and PUs showed a younger mean age and an earlier mean age of first treatment than NUs. As reported in the literature, younger subjects are the ones more frequently using cannabis and presumably, CUs and PUs received earlier clinical attention or showed an earlier full-blown expression of the disease due to a higher illness severity.

Another variable associated with a higher disease severity was the presence of psychiatric comorbidities. CUs showed an additional psychiatric comorbidity before and after the onset of OCD, although only pre-onset comorbidity rate was significantly higher in this subgroup compared to PUs and Nus. Additionally, CUs showed a significantly higher rate of pre-OCD onset comorbidity with bipolar disorder II, compared with NUs and PUs.

The comorbidity between OCD and bipolar disorder has been extensively investigated. In a recent meta-analysis, 13.5% of patients with OCD had a comorbid bipolar disorder, with more severe OCD symptoms during depressive episodes and decreased severity during manic or hypomanic episodes.[56] An international multicenter study conducted by the ICOCS reported that a higher number of hospitalizations, more frequent add-on therapy, and a higher severity of OCD symptoms were observed in the cases of comorbidity with bipolar disorder.[57] This is likely the case of the CUs subgroup investigated in the present study, reflecting a higher severity of the disease.

Conversely, a significantly higher rate of comorbidity with major depression disorder emerged in NUs compared to CUs and PUs. This result is quite unusual, considering that the co-occurrence of depression and cannabis use has strong evidence in the literature.[58] Indeed, given the high frequency of depression as a comorbidity, cannabis use may not be necessary to induce a depressive episode. Interestingly, PUs showed no history of major depression, but we believe that this could be a consequence of the limited sample size of this subgroup, and a large sample seems necessary to better understand the impact of this comorbidity.

Other clinical variables that have been consistently associated with greater disease severity in different psychiatric disorders including OCD[7] emerged to be more frequent in CUs compared to the other subgroups. In detail, CUs showed a longer DUI and an earlier AAO compared to the other subgroups. Despite the earlier

age of first treatment, CUs showed a longer DUI (more than 6 years) compared with NUs (5 years) and PUs (less than 4 years). Considering available literature on OCD, the DUI is high (up to around 10 years in adults) and a longer DUI has been correlated with poor treatment response and with considerable suffering for the individual and their families.[59–61] The reasons why patients who use cannabis have a longer DUI have not been investigated in patients with OCD thus far. Previous studies reported how cannabis use[62,63] and substance use disorder[64] were responsible for a longer duration of untreated psychosis. In the present sample, we might cautiously suggest that the same effects took place in the context of DUI in patients with OCD. Moreover, CUs showed an average AAO younger than 18 years (AAO around 16.3 years), and this has been identified by some authors as the "early onset" OCD phenotype, previously associated with male gender, a longer DUI,[65] a more frequent family history for OCD, as well as comorbidity with tic disorders.[66]

Similarly, psychometric questionnaires revealed a greater degree of OC, depressive, and general anxiety symptoms in CUs and PUs, compared to NUs. All these differences presumably reflect a higher disease burden in patients with cannabis use, although not reaching a statistically significant difference; a wider sample size might increase the statistical significance.

Outside cannabis use, CUs and PUs showed a higher tendency to other substances consumption, as highlighted by a significantly more frequent lifetime use of alcohol, cigarette smoking, and illicit substances compared with NUs. This association was maintained even in the closest temporal range, with alcohol and tobacco (the latter at a statistically significant level) more frequently used in PUs and CUs than NUs in the 6 months prior to study entry. The higher use of alcohol, cigarettes, and other substances might be a consequence of a substance-use diathesis manifested by cannabis users. On the other hand, it might reflect another effort to cope with OC symptoms (ie, alcohol use to reduce anxiety derived from obsessive thoughts) not adequately treated with conventional medications. Indeed, NUs showed to be more frequently on polypharmacotherapy, compared to CUs and PUs, which might reflect a better care of these patients, with consequently better response to their OC symptoms and therefore a lower tendency to reach for other substances to manage their OC symptoms.

Some limitations should be considered in the interpretation of the results. First, the limited sample size of the sample, in particular when divided in three subgroups, did not allow us to perform additional subgroups analyses that would have better described the impact of specific variables and might have reduced the power of the study and increased the margin of error. Moreover, another limitation of the study is represented by the possibility of type I error since no adjustment for multiple comparisons were performed. Our data showed cannabis users being the ones associated with more severe markers of illness with respect to OCD; however, this relationship might have been influenced by other variables (eg, a greater number of comorbid conditions), not being primarily related to cannabis use. Considering that cannabis is perceived as an illegal substance in Italy, patients might have been fearful of disclosing their use of cannabis to study investigators or have minimized how much of this substance that they used. Moreover, the cross-sectional/retrospective collection of data may have influenced the results, with longitudinal data being likely more informative. Additionally, lifetime/current cannabis or other substances use were the only variables related to substance use that have been collected. Indeed, other characteristics related to substance use

disorders (ie, impaired control, social impairment, risky use, and pharmacological implications derived from substances) were not investigated and deserve further study. Lastly, the limited sample size did not allow us to perform additional subgroup analyses that would have better described the impact of specific variables.

5. Conclusion

Overall, the specific pattern of substance use might contribute to the identification of a specific subgroup of patients with OCD that manifest a low level of harm-avoidance trait and more consistent impulsivity traits (although not measured in this study). Further specific investigations targeted to explore the impact of neuropsychological traits will need to be evaluated in future studies. Additionally, considering that these features might be associated with more severe clinical variables, clinicians should pay specific attention to substance use during the assessment to correctly identify and address these patients using specific therapeutic approaches. Considering the young age and the brain susceptibility of these patients, we believe additional attention must be raised at clinical and at societal levels. Lastly, potential interference of cannabis with pharmacokinetics of OCD medications is another area of potential concern that requires further evaluation.

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